



## Antibiotics, Topical Therapeutic Class Review (TCR)

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## FDA-APPROVED INDICATIONS<sup>1,2,3,4,5,6,7,8,9</sup>

Drug	Manufacturer	Indication(s)
bacitracin ointment (OTC)	generic	Prevention of skin and skin structure infections after a minor compromise in skin integrity such as minor burns or skin abrasion
bacitracin zinc ointment (OTC)	generic	Prevention of skin and skin structure infections after a minor compromise in skin integrity such as minor burns or skin abrasion
bacitracin zinc, neomycin, polymyxin B sulfate, hydrocortisone ointment (Cortisporin 1%) (OTC)	Monarch	Treatment of corticosteroid-responsive dermatoses with secondary infection
bacitracin zinc, neomycin, polymyxin B sulfate ointment (OTC) (Triple Antibiotic Ointment)	generic	Prevention of skin and skin structure infections, including wound management for skin abrasion and minor burn wound infection
bacitracin zinc, neomycin, polymyxin B sulfate, pramoxine ointment (OTC) (Triple Antibiotic Plus Ointment) (Antibiotic + Pain Relief Ointment)	generic	Prevention of skin and skin structure infections, including wound management for skin abrasion and minor burn wound infection
bacitracin zinc, polymyxin B ointment (Double Antibiotic Ointment) (OTC) (Polysporin Ointment)	generic	Prevention of skin and skin structure infections, including wound management of skin abrasion and minor burn wound infection
bacitracin zinc, polymyxin B (OTC) (Polysporin Powder)	J&J Consumer products	Prevention of skin and skin structure infections after a minor compromise in skin integrity such as minor burns or skin abrasion
gentamicin 0.1% cream (Rx)	generic	Treatment of minor bacterial skin infection including ecthyma, folliculitis, furunculosis, impetigo, pyoderma gangrenosum, sycosis barbae, infectious eczematoid dermatitis, pustular acne, pustular psoriasis, infected seborrheic dermatitis, infected contact dermatitis, infected excoriations, and bacterial superinfections of fungal or viral infections.
gentamicin 0.1% ointment (Rx)	generic	Treatment of minor bacterial skin infection including ecthyma, folliculitis, furunculosis, impetigo, pyoderma gangrenosum, sycosis barbae, infectious eczematoid dermatitis, pustular acne, pustular psoriasis, infected seborrheic dermatitis, infected contact dermatitis, infected excoriations and bacterial superinfections of fungal or viral infections.
mupirocin 2% cream (Rx) (Bactroban <sup>®</sup> )	generic GSK	Treatment of secondarily infected traumatic skin lesions (up to 10 cm in length or 100 cm <sup>2</sup> in area) due to susceptible strains of <i>Staphylococcus aureus</i> and <i>Streptococcus pyogenes</i>
mupirocin 2% ointment (Rx) (Bactroban <sup>®</sup> )	generic	Treatment of impetigo due to <i>S. aureus</i> and <i>S. pyogenes</i>
mupirocin 2% ointment (Centany <sup>®</sup> ) (Rx)	Medimetriks	Treatment of impetigo due to <i>S. aureus</i> and <i>S. pyogenes</i>
neomycin, polymyxin B sulfate, hydrocortisone cream (Cortisporin 0.5%) (OTC)	Monarch	Treatment of corticosteroid-responsive dermatoses with secondary infection
retapamulin 1% ointment (Altabax <sup>™</sup> ) (Rx)	Aqua	Treatment of impetigo due to <i>S. aureus</i> (methicillin-susceptible isolates only) and <i>S. pyogenes</i>
tetracycline (Viabecline <sup>®</sup> ) (OTC)	Accuria	Prevention of skin infection in minor cuts, scrapes, and burns.

OTC = over-the-counter; Rx = prescription required

Mupirocin calcium 2% ointment (Bactroban Nasal®) by GlaxoSmithKline is a paraffin-based formulation for intranasal use and is indicated in the eradication of nasal colonization with methicillin-resistant *S. aureus* (MRSA) in adult patients and healthcare workers.<sup>10</sup>

### FDA-Approved Microorganism Indications<sup>11,12</sup>

Drug	MRSA	MSSA	Staphylococcus epidermidis	Staphylococcus saprophyticus	Streptococcus pyogenes	Streptococcus sp.	Haemophilus influenzae	Pseudomonas aeruginosa
bacitracin ointment		X				X		
bacitracin zinc ointment		X				X		
bacitracin zinc, neomycin, polymyxin B sulfate, hydrocortisone ointment (Cortisporin 1%)		X				X	X	X
bacitracin zinc, neomycin, polymyxin B sulfate ointment (Triple Antibiotic Ointment, Triple Antibiotic Spray)		X				X	X	X
bacitracin zinc, neomycin, polymyxin B sulfate, pramoxine ointment (Triple Antibiotic Plus Ointment) (Antibiotic + Pain Relief)		X				X	X	X
bacitracin zinc, polymyxin B ointment (Double Antibiotic Ointment) (Polysporin Ointment)		X				X	X	X
bacitracin zinc, polymyxin B powder (Polysporin Powder)		X				X	X	X
gentamicin 0.1% cream		X	X		X		X	X
gentamicin 0.1% ointment		X	X		X		X	X
mupirocin 2% cream (Bactroban)	X	X	X	X	X			
mupirocin 2% ointment (Bactroban)	X	X	X	X	X			
mupirocin 2% ointment (Centany)	X	X	X	X	X			
neomycin, polymyxin B sulfate, hydrocortisone cream (Cortisporin 0.5%)		X				X	X	X
retapamulin 1% ointment (Altabax)		X			X			
tetracycline 3% ointment (Viabecline)	X*	X			X	X	X	

MRSA: methicillin-resistant *S. aureus*; MSSA: methicillin-sensitive *S. aureus*

\*Tetracyclines are not the drugs of choice for any type of staphylococcal infection.

## OVERVIEW

Skin and soft tissue bacterial infections are some of the most common issues with ambulatory care visits totaling approximately 14.2 million in 2005.<sup>13,14</sup> Most infections can be treated outpatient although physicians should be on alert for signs and symptoms of more severe infections. Therefore, clinical assessment of the severity of the infection, diagnosis, and knowledge of pathogen-specific antibiotic resistance is important.<sup>15</sup>

Skin and soft tissue infections can be caused by many different bacteria. Most infections are due to gram-positive microbes such as *Staphylococcus aureus*, *Streptococcus viridans*, *Enterococcus faecalis*, and group A (*S. pyogenes*) and B streptococci. Though not as common, gram-negative skin and soft tissue infections can occur due to *Haemophilus influenza*, *Pasteurella multocida*, *Aeromonas* species, *Clostridium* species, *Vibrio* species, *Mycobacterium* species, *Capnocytophaga* species, *Pseudomonas* species, *Proteus* species, and other anaerobes.<sup>16</sup> The most common skin infections are caused by *S. aureus*, *S. pyogenes*, or the normal skin flora.<sup>17</sup> However, *S. aureus* and *S. pyogenes* also happen to show the most antibacterial resistance.<sup>18,19</sup>

Patients who have compromised epidermis, poor hygiene, live in crowded conditions, have comorbidities, and have close contact with people having skin and soft tissue infections are at high risk of acquiring a skin and soft tissue infection themselves.<sup>20, 21</sup> Trauma to the epidermis exposes deeper tissue and allows for bacteria to enter the integumentary system. Other comorbidities which place patients at higher risk include eczema, psoriasis, superficial fungal infections, venous stasis, and lymphedema.<sup>22</sup> A CDC study demonstrated that invasive, life-threatening, methicillin-resistant *S. aureus* (MRSA) infections that began in hospitals declined 54% between 2005 and 2011, with 30,800 fewer severe methicillin-resistant staphylococcal infections. The study also showed 9,000 fewer deaths in hospital patients in 2005 versus 2011.<sup>23</sup>

Family physicians often treat patients with common skin infections such as impetigo.<sup>24</sup> The Infectious Diseases Society of America (IDSA) 2014 practice guidelines for the diagnosis and management of skin and soft-tissue infections recommend mupirocin (Bactroban) ointment or retapamulin ointment (Altabax) as the topical antibacterial drug of choice in the treatment of impetigo in infants 2 months and older and in adults.<sup>25,26</sup> Mupirocin ointment has activity against *S. pyogenes* and both methicillin-sensitive *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA), but some resistance has been reported.<sup>27</sup> Other topical agents, such as bacitracin and neomycin, are considerably less effective topical treatments when compared to mupirocin ointment. Topical therapy with mupirocin ointment is equivalent to oral systemic antimicrobials and may be used when lesions are limited in number. Patients who have numerous lesions or who are not responding to topical agents should receive oral antimicrobials effective against both *S. aureus* and *S. pyogenes*. Oral antibiotics, erythromycin, cephalexin, clindamycin, dicloxacillin, ciprofloxacin, levofloxacin, moxifloxacin, and ofloxacin are used to treat impetigo, and only effective for methicillin-sensitive *S. aureus* (MSSA).<sup>28,29,30</sup> Retapamulin (Altabax) was not available at the time of guideline development and publication.

## PHARMACOLOGY<sup>31,32,33,34,35,36,37</sup>

Mupirocin is a topical antibiotic that reversibly and specifically binds to bacterial isoleucyl transfer-RNA synthetase resulting in the inhibition of protein synthesis. Mupirocin is bactericidal at concentrations achieved by topical administration; however, the minimum bactericidal concentration (MBC) against relevant pathogens is generally 8-fold to 30-fold higher than the minimum inhibitory concentration (MIC).

Tetracycline is a topical antibiotic reversibly binding to the 30S subunit of the bacterial ribosome resulting in the inhibition of protein synthesis. Tetracyclines have activity against many gram-positive and gram-negative organisms.

Retapamulin (Altabax) is the first in a new class of antibacterial agents, the pleuromutilins, which inhibit normal bacterial protein biosynthesis by binding at the unique site (L3) on the ribosomal 50S subunit. This prevents the formation of active 50S ribosomal subunits by inhibiting peptidyl transfer and blocking P-site interactions at this site. Retapamulin is bacteriostatic against *S. aureus* and *S. pyogenes* at the retapamulin *in vitro* minimum inhibitory concentration (MIC) for these organisms. At concentrations 1,000 times the *in vitro* MIC, retapamulin is bactericidal against these same organisms.

A study that included 400 *S. pyogenes* isolates, including multidrug-resistant isolates, evaluated the *in vitro* activity of retapamulin compared to that of 16 other antimicrobial agents for topical and systemic use to treat acute bacterial skin infections. The isolates were divided into those obtained from skin lesions (n=144), blood (n=17), and other body sites such as the pharynx or ear fluid (n=239). Retapamulin showed potent *in vitro* activity against all clinical *S. pyogenes* isolates independently of the source of the sample and the resistance phenotype, including macrolide-, tetracycline-, fusidic acid-, quinolone-, and bacitracin-resistant isolates. The range of retapamulin susceptibility was between 0.015 and 0.12 g/mL, showing the highest intrinsic activity of the antimicrobial drugs often used topically. Based on MIC<sub>90</sub> values, retapamulin was at least 4-fold, 533-fold, 133-fold, and 1,066-fold more active than the most frequently used topical drugs, mupirocin, bacitracin, fusidic acid, and neomycin, respectively.

Bacitracin is a bacteriostatic against gram-positive and some gram negative bacteria and may also possess some bactericidal activity at certain concentrations. Bacitracin works by interfering with the mucopeptide transferring process and therefore prevents bacteria cell wall development.

Neomycin and gentamicin are aminoglycoside antibiotics with gram-positive and gram-negative bactericidal activity. Neomycin and gentamicin work by establishing irreversible binding to receptors present on the 30S ribosomal subunit of bacteria. The binding prevents the initiation complex between the bacterial messenger RNA and the ribosomal subunit which results in the misreading of the bacterial DNA and formation of nonfunctional proteins. As a result, bacteria containing these non-functional proteins die. Neomycin also inhibits DNA polymerase.

Polymyxin B is a bactericidal agent which binds to the cell membranes of gram-negative bacteria. Once bound, polymyxin destroys the bacterial cell membrane which results in cell membrane permeability and loss of metabolites. Pramoxine is a local anesthetic agent which blocks both the initiation and conduction of nerve impulses by decreasing the permeability of the neuronal membrane to sodium ions. This reversibly stabilizes the membrane and inhibits depolarization, resulting in the failure of a propagated action potential and subsequent conduction blockade.

Hydrocortisone is a topical corticosteroid that has anti-inflammatory properties that inhibit macrophage and leukocyte movement and activity in inflamed areas by reversing vascular dilation and permeability. Hydrocortisone also inhibits capillary production, collagen deposition, and keloid formation during the anti-inflammatory process.

## **PHARMACOKINETICS**<sup>38,39,40,41,42,43</sup>

Absorption of topically applied mupirocin is low. Data indicate more frequent occurrence of percutaneous absorption in children (90% of patients) than adults (44% of patients); however, mupirocin systemically absorbed is rapidly metabolized to the inactive metabolite, monic acid, which is renally excreted.

Pharmacokinetic characteristics of tetracycline (Viabecline) are not addressed in the prescribing information.

Systemic absorption following topical application of retapamulin to intact and abraded skin is low. Retapamulin (Altabax) is 94% protein bound. Retapamulin (Altabax) is metabolized by cytochrome (CYP) 3A4 hepatic enzymes by mono-oxygenation and di-oxygenation to multiple metabolites.

Bacitracin, neomycin, and polymyxin B have negligible systemic absorption after topical administration except when applied to large areas or long periods of time. Polymyxin B has little absorption even when applied to open wounds. However, systemic absorption has been reported when bacitracin, neomycin, or gentamicin has been applied to damaged epithelium. Gentamicin absorption across denuded skin had a rate of 5% but was not associated with systemic toxicity.

Absorption of topically applied pramoxine and hydrocortisone to intact skin is low, yet when skin permeability is increased by abrasions or ulcers, the absorption and efficacy improves. Topically applied hydrocortisone is metabolized by the skin.

## **CONTRAINDICATIONS/WARNINGS**<sup>44,45,46,47,48,49,50,51</sup>

Hypersensitivity to these agents or their components is considered a contraindication. These agents are for topical use only. They should not be used for ophthalmic, intranasal, oral, or intra-vaginally. They should be discontinued should sensitization or severe local irritation occur, and super-infection occur.

Retapamulin (Altabax) should not be used in the absence of proven or strongly suspected bacterial infection as it may increase the risk of the development of drug resistance bacteria. Epistaxis has been reported with retapamulin (Altabax) in the nasal mucosa.

Mupirocin (Bactroban) ointment contains polyethylene glycol (PEG) and should be avoided in conditions where absorption of large quantities of PEG is possible, especially if there is evidence of moderate to severe renal impairment; mupirocin (Bactroban) cream and mupirocin (Centany) ointment do not contain PEG base.

Tetracycline ointment (Viabecline) should not be used over large area of the body, for longer than 1 week duration unless directed by a physician, or in patients with hypersensitivity to any ingredient in the product. A physician should be consulted if the patient has deep or puncture wounds, animal bites, or serious burns. Tetracycline ointment is not for ophthalmic use.

Bacitracin and neomycin should be used with caution in patients with damaged epithelium, high risk for altered epithelium (e.g., elderly, children less than 2 years, infants, and neonates), renal impairment, or renal failure due to increased systemic exposure and risk for adverse effects such as nephrotoxicity and irreversible ototoxicity. Bacitracin should not be used for serious burns, puncture wounds, deep wounds, or animal bites unless directed by a physician. When absorbed systemically, neomycin has been reported to cause ototoxicity; therefore, application to damaged epithelium is cautioned. Prolonged use of bacitracin, neomycin, and polymyxin B may result in secondary infections; therefore, treatment greater than 7 days is not recommended.

Cortisporin ointment/cream is contraindicated in tuberculous, fungal, or viral lesions of the skin.

## **DRUG INTERACTIONS**<sup>52,53,54,55,56</sup>

The effect of concurrent application of mupirocin ointment or cream and other drugs has not been studied.

Oral ketoconazole was shown to increase AUC and Cmax of retapamulin by 81% after topical application to abraded skin. Systemic absorption of retapamulin is low; therefore, interactions with other CYP 450 substrates are not expected. The effect of concurrent application of retapamulin and other topical agents to the same area of skin has not been studied.

If absorbed systemically, bacitracin, gentamicin, neomycin, and polymyxin B may cause nephrotoxicity and neurotoxicity. Caution should be used in patients taking additional medications with nephrotoxic or neurotoxic adverse effects.

There are no reported drug interactions reported between topical hydrocortisone or pramoxine preparation and other medications.

## ADVERSE EFFECTS<sup>57,58,59,60,61,62,63,64,65</sup>

Drug	Application Site Irritation	Rash	Pruritus	Headache	Diarrhea	Nausea
bacitracin ointment	reported	reported	reported	nr	nr	nr
bacitracin zinc ointment	reported	reported	reported	nr	nr	nr
bacitracin zinc, neomycin, polymyxin B sulfate, hydrocortisone ointment (Cortisporin 1%)	reported	reported	reported	nr	nr	nr
bacitracin zinc, neomycin, polymyxin B sulfate ointment (Triple Antibiotic Ointment, Triple Antibiotic Spray)	reported	reported	reported	nr	nr	nr
bacitracin zinc, neomycin, polymyxin B sulfate, pramoxine ointment (Triple Antibiotic Plus Ointment) (Antibiotic + Pain Relief)	reported	reported	reported	nr	nr	nr
bacitracin zinc, polymyxin B ointment (Double Antibiotic Ointment) (Polysporin Ointment)	reported	reported	reported	nr	nr	nr
bacitracin zinc, polymyxin B (Polysporin Powder)	reported	reported	reported	nr	nr	nr
gentamicin 0.1% cream	reported	reported	reported	nr	nr	nr
gentamicin 0.1% ointment	reported	reported	reported	nr	nr	nr
mupirocin 2% cream (Bactroban)	< 1-3.6	1.1	2.4	1.7-3.6	nr	1.1-4.9
mupirocin 2% ointment (Bactroban)	1-1.5	< 1	1	nr	nr	< 1
mupirocin 2% ointment (Centany)	1	0.3	1	nr	nr	Nr
neomycin, polymyxin B sulfate, hydrocortisone cream (Cortisporin 0.5%)	reported	reported	reported	nr	nr	nr
retapamulin 1% ointment (Altabax)	1.6-1.9	nr	1.5	1.2-2	1.4-1.7	1.2
tetracycline (Viabecline)	nr	nr	nr	nr	nr	nr

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. nr = not reported.

## SPECIAL POPULATIONS<sup>66,67,68,69,70,71</sup>

### Pediatrics

Safety and effectiveness of mupirocin (Bactroban) ointment and retapamulin (Altabax) ointment have been established in patients aged 2 months and older, and 9 months and older, respectively. Mupirocin (Bactroban) cream has been FDA-approved in patients aged 3 months and older. Bacitracin, neomycin, and polymyxin B ointment have been FDA-approved in patients 2 years and older. Gentamicin cream and ointment have been FDA-approved for children over the age of 1 year.

Safety and effectiveness of Cortisporin cream/ointment in pediatric patients has not been established.

Labeling for tetracycline ointment (Viabecline) does not address safety and efficacy in pediatrics.

### Pregnancy

Mupirocin and retapamulin are Pregnancy Category B; bacitracin, hydrocortisone, neomycin, polymyxin B, and pramoxine are Pregnancy Category C. Gentamicin is categorized by the manufacturer as Pregnancy Category D but Briggs' *Drugs in Pregnancy and Lactation* categorizes it as Pregnancy Category C.

Labeling for tetracycline ointment (Viabecline) does not address safety and efficacy in pregnant women.

## DOSAGES<sup>72,73,74,75,76,77,78,79,80</sup>

Drug	Adult	Pediatrics	Availability
bacitracin ointment	Apply thin film 1 to 3 times daily (max 5 times daily)	Apply thin film 2 to 3 times daily (max 5 times daily)	500 U/1 gm ointment: 1, 3.5, 4, 14, 15, 28, 30, 60, 113, 120, 144, 454 gm
bacitracin zinc ointment	Apply thin film 1 to 3 times daily (max 5 times daily)	Apply thin film 2 to 3 times daily (max 5 times daily)	500 U/1 gm ointment: 1, 5, 14, 15, 28, 30, 120, 144, 454, 480 gm
bacitracin zinc, neomycin, polymyxin B sulfate, hydrocortisone ointment (Cortisporin 1%)	Apply thin film 2 to 4 times daily for a maximum of 7 days	--	bacitracin 400U/ neomycin 3.5gm/ polymyxin B 5000 U/1gm /hydrocortisone 10mg ointment: 15gm
bacitracin zinc, neomycin, polymyxin B sulfate ointment (Triple Antibiotic Ointment)	Apply thin film 1 to 3 times daily	Apply thin film 1 to 3 times daily for patients 2 years and older	bacitracin 400 U/ neomycin 3.5 mg/ polymyxin B 5000 U/1 gm ointment: 14, 15, 28, 30, 454 gm
bacitracin zinc, neomycin, polymyxin B sulfate (Triple Antibiotic Spray)	Apply as directed	--	bacitracin 400 U/ neomycin 3.5 mg/ polymyxin B 5000U 56 gm spray
bacitracin zinc, neomycin, polymyxin B sulfate, pramoxine ointment (Triple Antibiotic Plus Ointment) (Antibiotic + Pain Relief)	Apply thin film 1 to 3 times daily	Apply thin film 1 to 3 times daily for patients 2 years and older	bacitracin 500 U/ neomycin 3.5 mg/ polymyxin B 10,000 U/ pramoxine 10 mg/1gm ointment: 14, 28, 30 gm

**Dosages (continued)**

<b>Drug</b>	<b>Adult</b>	<b>Pediatrics</b>	<b>Availability</b>
bacitracin zinc, polymyxin B ointment (Double Antibiotic Ointment) (Polysporin Ointment)	Apply thin film 1 to 3 times daily	Apply thin film 1 to 3 times daily.	bacitracin 500 U/ polymyxin B 10,000 U/ 1 gm ointment: 14.2, 15, 28, 28.3, 30 gm
bacitracin zinc, polymyxin B (Polysporin Powder)	Apply a light dusting of the powder 1 to 3 times daily	Apply a light dusting of the powder 1 to 3 times daily.	bacitracin 500 U/ polymyxin B 10,000 U/ 10gm powder
gentamicin 0.1% cream	Apply 3 to 4 times daily	Apply 3 to 4 times daily for patients over 1 year old.	0.1% cream: 15, 30 gm
gentamicin 0.1% ointment	Apply 3 to 4 times daily	Apply 3 to 4 times daily for patients over 1 year old.	0.1% ointment: 15, 30 gm
mupirocin 2% cream (Bactroban)	Apply 3 times daily for 10 days; re-evaluate after 3 to 5 days if no clinical response	Apply 3 times daily for 10 days; re-evaluate after 3 to 5 days if no clinical response.	2% cream: 15, 30 gm
mupirocin 2% ointment (Bactroban)	Apply 3 times daily; re-evaluate after 3 to 5 days if no clinical response	Apply 3 times daily for patients 2 months to 16 years old. Re-evaluate after 3 to 5 days if no clinical response.	2% ointment: 1, 22 gm
mupirocin 2% ointment (Centany)	Apply 3 times daily; re-evaluate after 3 to 5 days if no clinical response	Apply 3 times daily for patients 2 months to 16 years old. Re-evaluate after 3 to 5 days if no clinical response.	2% ointment: 30 gm Kit -30 gm includes cloth tape and gauze pad
neomycin, polymyxin B sulfate, hydrocortisone cream (Cortisporin 0.5%)	Apply thin film 2 to 4 times daily for a maximum of 7 days	--	neomycin 3.5gm/ polymyxin B 10,000 U/1gm /hydrocortisone 5mg cream: 7.5gm
retapamulin 1% ointment (Altabax)	Apply twice daily for 5 days; total treatment area should not exceed 100 cm <sup>2</sup>	For patients 9 months to 17 years old: apply twice daily for 5 days; total treatment area should not exceed 2% body surface area.	1% ointment: 5, 10,15, 30 gm
tetracycline (Viabecline)	Apply a small amount to affected skin 1 to 3 times per day.  May cover with a sterile bandage  Stop use after 1 week if condition persists  Do no use longer than 1 week unless directed by a physician.	--	3% ointment: 5 mL, 15 mL  Keep refrigerated

## CLINICAL TRIALS

### Search Strategies

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled trials studying agents within this class for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

There are no published head to head trials comparing mupirocin and retapamulin (Altabax) in the treatment of impetigo. Due to the lack of studies, placebo-controlled trials have been included.

There are no published clinical study data for tetracycline 3% ointment (Viabecline) for the prevention of skin infection.

### **bacitracin ointment and white petrolatum**

Bacitracin was compared to white petrolatum to evaluate the incidence of wound infection, allergic contact dermatitis, and overall healing characteristics.<sup>81</sup> The study was a double-blinded, randomized study conducted in an outpatient dermatology and tertiary referral advanced surgical clinic. A total of 922 patients entered the study with 884 patients (440 white petrolatum patients and 444 bacitracin patients) completing the 4 week study. Thirty-four patients with 38 wounds (20 white petrolatum patients with 22 wounds and 14 bacitracin patients with 16 wounds) developed pus, erythema, or tenderness at the wound. Cultures were performed on the 38 wounds and 18 cultures produced no growth, 6 cultures produced coagulase-negative *Staphylococcus* species, and 14 produced pathogenic bacteria. The 14 cultures were from 13 patients with 9 (2%; 95% CI, 0.9% to 3.8%) patients being from the white petrolatum group and 4 patients (0.9%; 95% CI, 0.2% to 2.3%) being from the bacitracin group (95% for CI difference, -0.4% to 2.7%;  $p=0.37$ ). Eight of the infections from the white petrolatum and zero from the bacitracin group were due to *Staphylococcus aureus* ( $p=0.004$ ). No patients in the white petrolatum group developed allergic contact dermatitis versus 4 patients using bacitracin ( $p=0.12$ ). The study found that patients using white petrolatum did not experience a significant difference in infection incidence compared to the bacitracin group. There was a higher rate of *S. aureus* infection in the white petrolatum group compared to the bacitracin group although this is to be expected since this is the most common bacterial to infect the skin, and bacitracin will eliminate it. Overall, the study concluded bacitracin and white petrolatum have an equally low infection rate, and there were no clinically significant differences in healing between the white petrolatum and bacitracin groups on day 1 ( $p=0.98$ ), day 7 ( $p=0.86$ ), or day 28 ( $p=0.28$ ) after the procedure.

## **bacitracin zinc ointment, bacitracin zinc/neomycin/polymyxin B ointment, sulfadiazine cream, and petrolatum ointment**

A randomized, double-blind, placebo-controlled study was performed on 465 patients who presented to a military community hospital emergency department with a traumatic wound less than 12 hours old.<sup>82</sup> Thirty-nine patients were excluded from the study due to study protocol violations. There were more males in the study (n=300) compared to females (n=126), but the male-to-female ratios were similar between treatment groups. Patients were instructed to change the wound dressing and apply a blinded ointment to the wound every 8 hours until the return visit to the emergency department for removal of stitches. The wound depths and locations were also not statistically significant,  $p=0.66$  and  $p=0.89$ , respectively. Wound scrubbing ( $p=0.69$ ) and wound debridement ( $p=0.67$ ) were also not statistically different. The study concluded the wound infection rates for bacitracin zinc ointment (5.5%), bacitracin zinc/neomycin/polymyxin B ointment (4.5%), sulfadiazine cream (12.1%) were lower than petrolatum ointment (17.6%,  $p=0.0034$ ), and bacitracin zinc ointment and bacitracin zinc/neomycin/polymyxin B ointment had the lowest rate of wound infection.

## **mupirocin (Bactroban) cream and gentamicin cream**

A multicenter, randomized, double-blind study was conducted to compare the effectiveness of daily gentamicin and mupirocin cream in the prevention of peritoneal dialysis (PD) site infections.<sup>83</sup> Mupirocin treats *S. aureus* PD infections but does not decrease *Pseudomonas aeruginosa* or other Gram-negative infections which often result in morbidity and even death in PD patients. The study included 133 patients; 67 patients received gentamicin cream, and 66 patients received mupirocin cream. The study found the time to first catheter infection was longer in patients using gentamicin compared to mupirocin ( $p=0.03$ ). Likewise, the incident and prevalent patients had lower catheter infection rates with gentamicin compared to mupirocin and controlling for center and incident/prevalent status, only gentamicin had a lower catheter infection rate predictor (RR, 0.41; 95% CI, 0.22 to 0.78;  $p<0.007$ ). Gentamicin also showed a lower incidence of Gram-negative ( $p=0.03$ ) and Gram-positive ( $p<0.02$ ) infections. The frequency of peritonitis was lower in patients using gentamicin (0.34/year) compared to mupirocin (0.52/year;  $p=0.03$ ). Gentamicin use was also associated with a significant predictor of lower peritonitis rates when controlling for center and incident/prevalent patients (RR, 0.52; 95% CI, 0.29 to 0.93;  $p<0.03$ ). Similarly gentamicin users also had a lower gram-negative peritonitis rate ( $p<0.05$ ) when controlling for center and incident/prevalent status. In conclusion, researchers determined gentamicin cream was as effective as mupirocin in preventing *S. aureus* infections, and gentamicin reduced *P. aeruginosa* and gram-negative catheter exit site infections and decreased the rate peritonitis by 35%.

## **mupirocin (Bactroban) ointment and placebo**

The efficacy of mupirocin ointment in impetigo was assessed in a randomized, double-blind trial of adults and children aged 2 months and older.<sup>84</sup> Of the patients studied, 91% were between the ages of 2 months and 15 years. Patients received either mupirocin 2% ointment 3 times daily or placebo for 8 to 12 days. Clinical efficacy rates at the end of therapy in the population were 71% for mupirocin (n=49) and 35% for placebo (n=51). Pathogen eradication rates were 94% and 62%, in the mupirocin and placebo groups, respectively. There were no adverse events reported for the mupirocin group.

## **mupirocin (Bactroban) ointment and oral erythromycin**

Mupirocin ointment 3 times daily for 8 days was compared to oral erythromycin 40 mg/kg/day in a randomized open-label trial of patients 5 months to 13 years old with impetigo.<sup>85</sup> Patients were seen on days 4 to 5 of therapy, at end of therapy, and 7 days after therapy had ended. At the first visit, 24 of 30 children in the mupirocin and 14 of 32 children in the erythromycin group were cured or had at least a 75% reduction in size of lesions. At the completion of the study, all 29 patients in the mupirocin group and 27 of the 29 patients in the erythromycin group were cured. Mild diarrhea developed in the erythromycin group. The study concluded that mupirocin appears to be safe and effective in the treatment of impetigo in children.

A prospective double-blind, randomized trial, compared topical mupirocin with oral erythromycin to determine the prevalence of erythromycin-resistant *S. aureus* strains in impetigo and whether an increased rate of failure of erythromycin was associated with such resistance.<sup>86</sup> A total of 102 patients between 3 months and 15.5 years old were enrolled and received erythromycin 50 mg/kg/day or mupirocin 2% ointment, plus respective placebos for 7 days. *S. aureus* was cultured from 88% of patients of which 28% were erythromycin-resistant. In all cases *S. aureus* was sensitive to mupirocin. Only patients with erythromycin-resistant *S. aureus* strains had unfavorable courses compared with mupirocin (failure rate 47% versus 2%, respectively). Patients with erythromycin-susceptible *S. aureus* strains who received erythromycin had a failure rate of 8%. In 4 patients, *S. aureus* strains initially susceptible to erythromycin became resistant during treatment. The study concluded that erythromycin-resistant *S. aureus* strains were commonly isolated from impetigo lesions in the study region.

## **mupirocin (Bactroban) cream and oral cephalexin**

A randomized, double-blind, double-dummy, multicenter trial of 159 patients with secondarily infected eczema and a total skin infection rating scale score of 8 or greater compared mupirocin 2% cream 3 times daily to oral cephalexin 250 mg 4 times daily for 10 days.<sup>87</sup> Per protocol clinical success, defined partly as a patient with a response of improvement in the skin infection rating scale, was similar in both arms: 89% and 82%, in the mupirocin and cephalexin groups, respectively (95% CI, -8.4 to 22.5; p=0.29). Bacteriological success defined as eradication, improvement, or colonization of bacteria at end of therapy, was higher in the mupirocin group versus cephalexin, 50% versus 28%, respectively (p=0.005). Both drugs were well tolerated. Diarrhea and nausea were common adverse effects.

Two identical randomized, double-blind studies of 706 patients with secondarily infected wounds (small lacerations, abrasions, or sutured wounds) compared mupirocin 2% cream topically 3 times daily to oral cephalexin 4 times daily for 10 days.<sup>88</sup> Clinical success at follow-up was the same in the 2 groups, 95.1% versus 95.3% in the mupirocin cream and the cephalexin groups, respectively (95% CI, -4% to 3.6%; p=0.89). The intention-to-treat success rate was 83% in both groups. Bacteriologic success at follow-up was similar in the 2 groups: 96.9% in the mupirocin cream versus 98.9% in the cephalexin groups (95% CI, -6% to 2%; p=0.22). Adverse event profile was similar; however, more diarrhea in the cephalexin group was reported.

Mupirocin cream was compared to oral cephalexin in 2 randomized, double-blind, double-dummy studies of secondarily infected skin lesion studies.<sup>89</sup> In the studies, 93 pediatric patients aged 2 weeks to 16 years old were randomized to mupirocin 2% cream 3 times daily or oral cephalexin 250 mg 4 times daily for patients > 40 kg or 25 mg/kg/day oral suspension in 4 divided doses for patients ≤ 40 kg

for 10 days. At follow-up (seven to 12 days after therapy), clinical efficacy was achieved in 97.7% and 93.9%, in mupirocin and cephalexin, respectively.

### **retapamulin (Altabax) and placebo**

The safety and efficacy of retapamulin were evaluated in a randomized, double-blind, placebo-controlled, multicenter study enrolling 213 patients.<sup>90, 91</sup> A total of 210 adults and children aged 9 months and older with impetigo (up to 100 cm<sup>2</sup> in total area- up to 10 lesions - or a total body surface area not exceeding 2%) were randomized to retapamulin 1% ointment or placebo applied twice daily for 5 days. Patients with underlying skin disease or skin trauma with evidence of secondary infections were excluded from the study. Most of the patients (78%) were less than 13 years old. Clinical success rates, defined as response of impetigo at 7 days where no further antimicrobial treatment was required, were higher in the retapamulin group versus placebo, 85.6% versus 52.1% for the intent to treat population, respectively (95% CI, 20.5 to 46.5; p<0.0001). Pruritus at the application site was reported by 6% and 1% of the retapamulin and placebo groups, respectively.

## **META-ANALYSES**

A meta-analysis of 57 randomized controlled trials including 3,533 patients, studied comparisons of 20 oral and 18 topical treatments for impetigo.<sup>92</sup> Topical antibiotics had better cure rates than placebo (pooled OR 6.49, 95% CI, 3.93 to 10.73). There was no significant difference between topical mupirocin and topical fusidic acid (pooled OR of mupirocin versus fusidic acid 1.76, 95% CI, 0.69 to 2.16). Fusidic acid is not commercially available in the United States. Topical mupirocin had better cure rates compared to oral erythromycin (OR 1.22, 95% CI, 1.05 to 2.97). There were no significant differences in cure rates among other topical and oral antibiotics studied.

Another meta-analysis of 16 randomized controlled trials, including double-blinded and observer-blinded trials, indicated that topical antibiotics were more effective than placebo (OR 2.69, 95% CI, 1.49 to 4.86) for the treatment of impetigo.<sup>93</sup> There was weak evidence favoring topical antibiotics over some oral antibiotics such as erythromycin (OR 0.48, 95% CI, 0.23 to 1). There was no significant difference between the topical therapies, mupirocin and fusidic acid. (OR 1.76, 95% CI, 0.77 to 4.03).

## **SUMMARY**

Skin and soft tissue bacterial infections are a common problem seen in many clinical practices. Most skin and soft tissue infections can be managed on an outpatient basis and are easily treatable; however, physicians should observe for any signs or symptoms of severe infection. Several bacterial microorganisms can infect the skin and soft tissue, but the most common agents are *S. aureus* and group A (*S. pyogenes*) streptococci. In general, the selection of topical antibiotic agent will be dependent on the probable microorganism causing the infection.

The Infectious Diseases Society of America (IDSA) 2014 practice guidelines for the diagnosis and management of skin and soft-tissue infections recommend mupirocin (Bactroban) ointment and retapamulin ointment (Altabax) as the topical antibacterial drugs of choice in the treatment of impetigo in infants 2 months and older and adults.

Mupirocin (Bactroban) ointment and retapamulin (Altabax) have not been studied in head to head trials in the treatment of impetigo so it is unclear if retapamulin (Altabax) is more effective than mupirocin. Retapamulin (Altabax) is not FDA-approved for use in infections caused by MRSA. At this

time, retapamulin has only been compared to placebo. Retapamulin (Altabax) has an advantage in that its dosage regimen is twice daily versus that of mupirocin, which is 3 times daily; however, total treatment area for retapamulin should not exceed 100 cm<sup>2</sup> in adults or 2% of total body surface area (BSA) in children and adolescents. Retapamulin (Altabax) is an alternative to mupirocin ointment for the topical treatment of impetigo due to *S. aureus* (methicillin-susceptible isolates only) and *S. pyogenes*. Impetigo is usually a self-limiting skin infection, but resistance patterns should be taken into account in the choice of therapy.

Mupirocin (Bactroban) cream is FDA approved for the treatment of secondary infected traumatic skin lesions due to susceptible strains of *S. aureus* and *S. pyogenes*. It is not indicated for impetigo; however, mupirocin ointment is FDA approved for the treatment of impetigo due to *S. aureus* and *S. pyogenes*. Mupirocin (Bactroban) cream is not in a polyethylene glycol (PEG) base like mupirocin (Bactroban) ointment. PEG can be absorbed from open wounds and damaged skin therefore should be avoided in patients with moderate to severe renal impairment. Direct comparative trials of the cream and ointment formulations are lacking, and they are not considered interchangeable.

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